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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/773,736	02/02/2001	Hirokazu Kubota	Q62542	6936

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EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/773,736

Applicant(s)

KUBOTA ET AL.

Examiner

Deepak R Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-6,8-10,15,16,18,19,21 and 26-47 is/are pending in the application.
- 4a) Of the above claim(s) 8 and 18 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 37 is/are allowed.
- 6) ☒ Claim(s) 1,4-6,9,10,15,16,19,21,26-36 and 38-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 12, 2004 has been entered.

Claims 1, 4-10, 15-16, 18-19, 21 and 26-47 are currently pending in this application.

Election/Restriction

Applicant elected the species of Example 1, 4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-4-methylthiazole-5-carboxamidide in Paper No. 7. As the elected species was not found in the prior art, the search was expanded to a subgenus of structural formula (I) wherein D is 1H-pyrazol-1-yl; B is 1,4-phenylene; X is -NH-CO- and A is as defined in the claims, and art was found. As per the guidelines of election of species in MPEP 803.02, claims 8 and 18 (wherein D is 1H-pyrazol-5-yl); and the generic subject matter of D, B and X other than as indicated above of the remaining pending claims, is withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 26, 27, 32-34, 39-41 and 44-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis and bronchial asthma, does not reasonably provide enablement for a method of treating a disease associated with calcium release-activated channels generally; a method of treating a disease associated with IL-2 production generally; a method of treating an allergic, inflammatory or autoimmune disease generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. In the instant case, the specification is not enabling based on one or more of the above factors.

The instant claims recite method for the treatment of diseases associated with calcium release-activated calcium channels; IL-2 production; and allergic, inflammatory or autoimmune diseases, and the specification fails to enable one skilled in the art for the recited use. The claims cover 'disorders' that are known to exist and those that are yet to be discovered and therefore, the use of the term is extremely broad. The use disclosed in the specification is as therapeutic agents for the treatment of various diseases listed in pages 26-27, which include several allergic, inflammatory and autoimmune diseases. The specification does not provide any guidance

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regarding how to identify the subject 'in need of the claimed method of treatment' or 'susceptible to the disease'. *In vitro* test procedures for measuring the CRACC inhibitory activity and Inhibitory effect on IL-2 production of the compounds are provided on pages 28-32 and IC_{50} values for some compounds are provided. There is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the various disorders of the instant claims. The data provided is insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. The area of receptor interactions is highly structure specific and unpredictable. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Regarding Ca^{2+} mechanism, Putney (J. Cell Science 2001) provide that "Clearly much still needs to be done if we are to sort out these possibilities and better understand the regulation of this major Ca^{2+} signaling pathway" (see page 2227). Regarding inhibitors or IL-2 receptors, McDyer et al. (The J. Immunology 2002), indicate that "their therapeutic efficacy has not been fully elucidated" (see the abstract). An online reference discloses the unpredictability of IL-2 therapy "IL-2 appears to have a role in the treatment of metastatic melanoma patients. Studies to be completed over the next several years will more clearly define and refine this role" (see <http://www.skincancer.org/melanoma/interleukin.php>).

Further, there is no disclosure regarding how the patient in need of the treatment is identified and further, how types of allergic, inflammatory disorders, autoimmune disorders are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific

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arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the inhibitory data provided is insufficient for one of ordinary skill in the art in order to extrapolate to all types of disorders of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Enablement for the scope of "treatment of inflammatory disorders" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall

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something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammatory disorders. It establishes that it is not reasonable to any agent to be able to treat inflammatory disorders generally.

Elgert (Immunology, 1996) indicate factors that effect autoimmune diseases include dysfunction in cytokine production, thymic defects, genetic factors, hormonal factors, etc. The author further comments regarding insulin dependent diabetes mellitus that “The only diabetes treatment is replacement therapy through insulin injections” (page 323); “Systemic lupus erythematosus (SLE) is an inflammatory connective tissue disease of unknown cause” (page 324). Wachlin et al. (Journal of Autoimmunity 2003) indicate that “The pathogenesis of

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autoimmune diabetes has been studied extensively but the mechanisms involved in the beginning of β -cell destruction remain still unclear” (see page 307-308).

The therapeutic method of the instant claims includes treatment of inflammatory bowel disease including Crohn’s disease and ulcerative colitis, which have been proven very difficult to treat because ‘there is no known cause’ (see The Merck Manual). Bremner et al. (Expert Opin. Pharmacother. 2002) provide that “New therapies that affect immunomodulation offer the possibility of disease control in those unresponsive to conventional therapy and may reduce the need for further surgery. However, these treatments remain to be fully evaluated” (see page 820). Singh et al. (British Journal of Surgery, 2001) provide that ‘the etiology and pathogenesis of inflammatory bowel diseases are incompletely understood’ (see page 1558). Robinson (Eur. J. Surg. 1998) indicates that “Despite the growing list of medications and formulations prompted for the treatment of IBD, no single drug or recognized combination has yet been confirmed as dependably clinically effective”; “All physicians who care for UC and CD patients enthusiastically await more optimal regimens for these challenging disorders” (see page 90). This is indicative of the unpredictability related to the treatment of inflammatory bowel diseases.

Further, the claims recite treatment of allergic diseases. The number and complexity of allergenic triggers rise with each year that passes, the incidence of allergic diseases rises, and diseases like eczema have now reached epidemic proportions with no end in sight. Doctors and researchers struggle to find an effective therapeutic remedy, but so far have achieved only palliative remedies. Allergic reactions or diseases may involve any part of the body; the most frequently involved are the nose and chest with resultant symptoms of hay fever, rhinitis or asthma, respectively. The skin and eyes also commonly show allergic symptoms. Anaphylactic

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shock is a severe allergy, which affects many organs at the same time causing a rapid decrease in blood pressure, fainting and, occasionally, death. Allergies come in a variety of forms and vary in severity from mildly bothersome to life-threatening and there is no single method of treatment which is known to be effective against all types of allergies.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-10, 15-16, 18-19, 21, 26-36 and 38-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the claims, in the definition of A, it is recited that “mono-, di- or **tri-cyclic** fused heteroaryl selected from”, however, there are no tricyclic heteroaryl groups in the list. The discrepancy is observed in all independent claims and the dependent claim 4.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4-6, 9, 10, 15-16, 19, 21 and 26-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Betageri et al., U.S. Patent No. 6,506,747 (effective filing date: June 5, 1998). The instantly claimed compounds read on reference disclosed compounds, see the structural formula I in col. 6 wherein L is -NH-CO- and the compounds disclosed in the Examples and the compounds of Table 1. The reference teaches that the compounds are useful in treating a variety of disorders including inflammatory diseases, autoimmune diseases, allergies, etc. see col. 18-19.

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Applicant's claim for priority benefit over foreign application JP 9-279093 filed October 13, 1997 is acknowledged. Applicant filed the English language translation of the priority application on July 1, 2003. The instant claims are not eligible for the priority benefit because the foreign application does not fully disclose the claimed invention. Particularly, support is not found for the following elements of instant claims:

1. A is defined to be a 'tri-cyclic fused heteroaryl' in instant claims. The priority document defines A to be 'a heteroaryl which may be condensed' and further defines the condensed heteroaryl to be "a group obtained by condensing one benzene ring with a five- or six-membered heteroaryl group or a bicyclic group obtained by condensing two five- or six-membered heteroaryl rings with each other" (see page 23) and provides examples which include bicyclic groups (see page 24).
2. As per the structural formula (I) of the instant claims, the pyrazole ring D may be attached to ring B through any of the ring members 1-5. The priority document does not disclose the structural formula (I) of the instant claims. The structural formulae containing pyrazolyl groups disclosed in pages 20, 31 and 91-100 of the priority document are all drawn to compounds wherein D is pyrazol-1-yl or pyrazol-5-yl group. The priority document does not provide any disclosure regarding compounds wherein D is pyrazol-4-yl.
3. In the instant D is defined as 'pyrazolyl which may have 1 to 3 substituents'. The priority document defines D to be 'a heteroaryl group which may be substituted', however, the specific disclosure of pyrazolyl compounds in pages 20, 31, 91-100 contain two

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substituents. There is no disclosure in the priority document of compounds wherein the pyrazolyl is substituted by three substituents.

4. In the instant claims, in the definition of A, the aryl and heteroaryl groups are recited to contain "one or more substituents". The priority document defines A to be 'an aryl or heteroaryl group which may be substituted', however, does not support the instant recitation of 'one or more substituents'. All the compounds disclosed in the priority document have at the most one substituent.

Allowable Subject Matter

Claim 37 is allowed. Claim 38, 42 and 43 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. These claims are eligible for the priority benefit as the priority document discloses the compound recited in the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-

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0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

May 28, 2004